Editorial Note: This manuscript has been previously reviewed at another journal that is not operating a transparent peer review scheme. This document only contains reviewer comments and rebuttal letters for versions considered at *Nature Communications*.

REVIEWERS' COMMENTS:

Reviewer #1 (Remarks to the Author):

The authors nicely replied to our comments and changed the statements in the manuscript accordingly. Maybe as expected, it is now apparent that chain termination does not play a role in the mechanism of action and the main mechanism of Favipiravir is actually increased mutagenesis, consistent with the literature.

I recommend publication of this important work after minor adjustments that I leave to the editor to judge:

The title is not informative and should be changed to better reflect the contents.

The introduced speculation that primer-template substrates are less well extended compared to hairpin substrates because unstructured portions of nsp8 might unwind the RNA duplex is not supported and may be deleted.

Reviewer #2 (Remarks to the Author):

I previously reviewed this manuscript by Shannon et al for Nature. In this revised version, the authors have addressed my comments in sufficient detail by either clarifying the text and/or providing additional data. Any further points I had have been covered by comments to the other reviewers. Overall, I feel that the current data support the claims made in the manuscript and that the manuscript would be a valuable addition to the field, in particular in light of the current pandemic

Rapid incorporation of Favipiravir by the fast and permissive viral RNA polymerase complex results in SARS-CoV-2 lethal mutagenesis
Shannon et al., 2020

Response to Referees

REVIEWERS' COMMENTS:

Reviewer #1 (Remarks to the Author):

The authors nicely replied to our comments and changed the statements in the manuscript accordingly. Maybe as expected, it is now apparent that chain termination does not play a role in the mechanism of action and the main mechanism of Favipiravir is actually increased mutagenesis, consistent with the literature.

I recommend publication of this important work after minor adjustments that I leave to the editor to judge:

The title is not informative and should be changed to better reflect the contents. Title has been changed

The introduced speculation that primer-template substrates are less well extended compared to hairpin substrates because unstructured portions of nsp8 might unwind the RNA duplex is not supported and may be deleted. The statement ‘or that can perhaps be strand separated by interactions with unfolded sections of nsp8’ has been removed from line 103

Reviewer #2 (Remarks to the Author):

I previously reviewed this manuscript by Shannon et al for Nature. In this revised version, the authors have addressed my comments in sufficient detail by either clarifying the text and/or providing additional data. Any further points I had have been covered by comments to the other reviewers. Overall, I feel that the current data support the claims made in the manuscript and that the manuscript would be a valuable addition to the field, in particular in light of the current pandemic. No changes requested